学　位　論　文

COMT Val 108/158 Met polymorphism and treatment response to aripiprazole in patients with acute schizophrenia

（統合失調症急性期における *COMT* Val 108/158 Met 遺伝子多型と Aripiprazole 治療反応性）

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論　文　内　容　要　旨（和文）

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統合失調症治療の薬剤反応性について薬理遺伝学的研究が行われている。COMT は神経伝達物質の代謝酵素で Val108/158Met(rs4680)多型には酵素活性差がある。Met/Met 型は抗精神病薬反応性が高いが、aripiprazole（ARP）を用いた研究はない。Homovanillic acid (HVA)および 3-methoxy-4-hydroxyphenylglycol (MHPG)は各々ドーパミン、ノルアドレナリンの代謝産物で、血漿 HVA、MHPG は中枢神経系のそれを一定の割合で反映し、血漿 HVA 濃度は抗精神病薬反応性の予測因子とされる。統合失調症治療にてこの遺伝子多型と ARP 治療反応性および神経伝達物質との関連は明らかでないため検討を行った。

DSM-Ⅳ-TR 診断基準を満たす統合失調症 40 名で、未服薬または 2 週間以上抗精神病薬を内服しておらず、Positive and Negative Syndrome Scale (PANSS)合計 score が 80 点以上、かつ少なくとも 2 つの精神病サブスケールにて 4 点以上を満たす者を対象とし、6 週間 ARP 投与した。症状評価は PANSS、Clinical Global Impression (CGI)-S、CGI-I を用い、入院時の PANSS total score から 30%減少，または CGI-I で中等度以上改善した者を治療反応者とした。入院時と 6 週目に採血し、血漿 HVA・MHPG 濃度を高速液体クロマトグラフィー法にて測定、遺伝子多型は PCR-RFLP 法にて分析した。本研究は福島県立医科大学の倫理委員会で承認され対象者からは書面にて同意を得た。

血漿 HVA 濃度は治療反応群のみ低下し、血漿 MHPG 濃度は両群とも低下した。遺伝子型は Val/Val 型 23 名、Val/Met 型 13 名、Met/Met 型 4 名であった。入院時遺伝子多型間の PANSS 各 score、CGI-S、モノアミン代謝産物濃度に有意差はなかった。遺伝子多型間で治療反応率に有意差はなかったが、PANSS total score、PANSS general psychopathology score において遺伝子型×時間の有意な交互作用（P=0.009、P=0.007）、PANSS negative score においても同様の傾向を認めた（P=0.065）。血漿モノアミン代謝産物濃度は遺伝子多型との有意な関連はなかった。

本研究は急性期統合失調症にてこの遺伝子多型が ARP 治療反応性および血漿モノアミン代謝産物濃度に及ぼす影響をみた初の研究である。抗精神病薬はドーパミン D2 受容体遮断により拮抗作用を発揮する。Met 型は Val 型よりも酵素活性が低いためドーパミン過剰状態となり拮抗作用は発揮されやすくなり、遺伝子多型による治療反応の違いが部分的に説明される。本研究では遺伝子多型とドーパミン過剰とされる陽性症状の改善との関連を認めず、更なる検討が必要である。前頭葉機能はドーパミンが適度なレベルで存在することが望まく、非定形抗精神病薬はドーパミン D2 受容体とセロトニン 2A 受容体を遮断し前頭前皮質のドーパミン伝達を調整し、さらに ARP はドーパミン D2 受容体部分作動薬という薬理作用を通しドーパミン機能を調整していると想定されるため、Met/Met 型が ARP に反応しやすいことは、前頭葉のドーパミン機能調節を介した認知機能の改善と関係がある可能性がある。モノアミン代謝産物濃度変化と遺伝子多型との関連がなかったが、COMT はモノアミン代謝酵素で抗精神病薬が直接作用せずモノアミン代謝産物への影響は大きくないと想定される。本研究から Val108/158Met 多型は ARP への治療反応性と関連し、Met/Met 型は Val 型よりも症状改善が大きいことが示された。

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【Introduction】

統合失調症には様々な遺伝・環境要因が存在し、ドーパミンを含む脳内神経伝達物質がその発症や症状に関わっている。抗精神病薬は統合失調症の治療に重要な役割を担っているが、薬剤反応性には一定の個人差が存在し、薬剤反応性のマーカーや予測因子解明のために薬理遺伝学的研究が行われてきている。

現在までのメタアナリシスにより、抗精神病薬の治療反応性と関連がある遺伝子多型として、ドーパミン D2 受容体-141C Ins/del (rs1799732)多型、セロトニン 2A 受容体 T102C (rs6313)多型、セロトニン 1 A 受容体 C1019G (rs6295)多型、Catechol-*O*-methyltransferase（COMT）Val 108/158 Met (rs4680)多型が報告されている。

COMT はドーパミン、ノルアドレナリン等の神経伝達物質や L-dopa 等の薬物の代謝酵素である。*COMT* Val 108/158 Met (rs4680)遺伝子多型の Val 型は Met 型よりも 3-4 倍酵素活性が高いとされ、神経伝達物質や薬物の動態に影響を与えていると考えられる。最近のメタアナリシスでは Met/Met 型を有する者は統合失調症治療において抗精神病薬への反応性が高いと報告されているが、この研究の抗精神病薬には他の薬剤と異なるドーパミン D2 受容体部分アゴニスト作用を有する aripiprazole（ARP）は含まれていない。

Homovanillic acid (HVA)および 3-methoxy-4-hydroxyphenylglycol (MHPG)はそれ

ぞれドーパミン､ノルアドレナリンの主要代謝産物であり、血漿中の HVA、MHPG はそれぞれ中枢神経系の HVA、MHPG を一定の割合で反映していることが報告されており、血漿 HVA 濃度は抗精神病薬への治療反応性や症状改善の予測因子であると考えられている。

統合失調症治療において、*COMT* Val108/158Met 多型と ARP への治療反応性および神経伝達物質との関連はまだ明らかではない。今回われわれは急性期統合失調症患者において *COMT* Val108/158Met 多型と ARP への治療反応性および血漿モノアミン代謝産物濃度との関連を検討したので報告する。

【Materials and Methods】

DSM-□-TR の診断基準を満たす日本人の統合失調症患者で、未服薬または 2 週間以上抗精神病薬を内服していない者を対象とした。対象は Positive and Negative Syndrome Scale (PANSS)合計 score が 80 点以上、かつ少なくとも 2 つの精神病サブスケールにて 4 点以上を満たす者とし、アルコール／薬物依存、頭蓋内器質性疾患の者は除外した。対象者には 6 週間 ARP の投与を行い、用量は担当医の判断で調節可能とし、併用薬については不安・焦燥、不眠や錐体外路症状に対してベンゾジアゼピン系薬剤および抗パーキンソン薬を併用可能とした。症状評価には PANSS、Clinical Global Impression (CGI)-S、CGI-I を用い、入院時

の PANSS total score から 30%減少，または CGI-I で中等度以上改善した者を治療反応者と定義した。

入院時および 6 週目に採血を行い、血漿 HVA および血漿 MHPG 濃度を高速液体クロマトグラフィー法にて測定した。*COMT* Val108/158Met 多型は PCR-RFLP 法にて分析した。本研究は福島県立医科大学の倫理委員会で承認され、対象者からは書面を用いて同意を得た。

【Results】

40 名の対象者のうち 39 名が試験を完了し、1 名は効果不十分にて中断となった。40 名中治療反応者は 16 名であり、ベンゾジアゼピン系薬剤、抗コリン薬の使用は 40 名中それぞれ 29 名 (72.5%)、10 名 (25%)であった。治療反応群では治療前後で血漿 HVA 濃度が低下したのに対し、非反応群では変化は認められなかった。血漿 MHPG 濃度は治療反応群および非反応群の両群で治療後に低下した。*COMT* Val108/158Met 多型については、40 名のうち、23 名が Val/Val 型、13 名が Val/Met 型、4 名が Met/Met 型であり、この分布はハーディワインベルグ平衡にあった。ベースラインにおいて、*COMT* Val108/158Met 遺伝子多型の 3 群間で PANSS 各 score、CGI-S、モノアミン代謝産物濃度に有意差は認めなかった。

COMT Val108/158Met 多型の 3 群間で治療反応率に有意差は認めなかったが、

PANSS total score、PANSS general psychopathology score において遺伝子型×時間の有意な交互作用（$p = 0.009$、$p = 0.007$）を認め、また PANSS negative score においても同様の傾向が認められた（$p = 0.065$）。

一方、血漿モノアミン代謝産物濃度については、*COMT* Val108/158Met 多型との有意な関連は認めなかった。

【Discussion】

本研究は、急性期統合失調症において *COMT* Val108/158Met 多型が ARP への治療反応性および血漿モノアミン代謝産物濃度に及ぼす影響を調べた初めての研究である。今回の結果は Met/Met 型において ARP 治療による統合失調症症状の改善が大きいことを示しており、Met/Met 型の者は Val 型を有する者よりも治療反応が良いというメタアナリシスの結果を裏付けるものであった。

COMT Val108/158Met 多型による治療反応の違いは、COMT の酵素活性という点で部分的に説明可能かもしれない。Val 型は Met 型よりも 3-4 倍酵素活性が高く、Met/Met 型は COMT 活性が低いためドーパミン代謝を効果的に行えず、ドーパミンの過剰状態を引き起こしている可能性がある。抗精神病薬はドーパミン D2 受容体の遮断によりアンタゴニスト作用を発揮するが、ドーパミン過剰状態が存在していればこのアンタゴニスト作用はより発揮されやすいものと考え

られる。しかしながら、本研究では *COMT* Val108/158Met 遺伝子多型と、ドーパミン過剰により引き起こされると考えられる陽性症状の改善とは関連が認められなかったため、さらなる検討が必要である。

また、ドーパミン機能の逆 U-curve 仮説によると、ドーパミン過剰は前頭葉機能の working memory を悪化させ、一方でドーパミン不足は認知機能低下を引き起こすと報告されており、ドーパミンが適度なレベルで存在することが望ましいとされている。ARP を含む非定形抗精神病薬はドーパミン D2 受容体とセロトニン 2A 受容体を遮断し、前頭前皮質のドーパミン伝達を調整していると想定されている。加えて、ARP はドーパミン D2 受容体部分アゴニストというユニークな薬理作用を通して前頭前皮質のドーパミン機能を調整していると考えられている。これらのことから、*COMT* Val108/158Met 遺伝子多型の Met/Met 型において ARP への反応が良いことは、前頭葉におけるドーパミン機能の調節を介した認知機能の改善関係があるとも考えられ、この結果統合失調症症状の改善につながった可能性がある。

一方、モノアミン代謝産物濃度については、*COMT* Val108/158Met 多型と血漿 HVA および MHPG 濃度の変化との関連はみられなかった。COMT はドーパミンを含むモノアミンの代謝酵素であり、抗精神病薬の直接作用部位ではないため、*COMT* Val108/158Met 多型によるモノアミン代謝産物への影響は大きくないと想

定される。

本研究から、*COMT* Val108/158Met 多型は他の抗精神病薬と同様 ARP への治療反応性と関連し、Met/Met 型においては Val 型を有する者よりも症状の改善が大きいことが示された。対象者が少ないため、より大きなサンプルサイズでのさらなる研究が必要である。

CONTENTS

Introduction

Schizophrenia is a heterogeneous disease that is influenced by various genetic and environmental factors. Neurotransmitters in brain including dopamine are associated with the onset, development, and psychopathology of schizophrenia. Antipsychotics play a critical role in the treatment of schizophrenia, there are considerable inter-individuals differences in the treatment response to antipsychotics. Pharmacogenetic studies have focused on various genes to identify meaningful predictors for treatment response to antipsychotics. Previous meta-analyses showed significant associations between the treatment response to antipsychotics and the -141C Ins/del (rs1799732) polymorphism in *DRD2* [1], the T102C (rs6313) polymorphism in *5HT2A* [2], the C1019G (rs6295) polymorphism in *5HT1A* [3], and Val 108/158 Met (rs4680) polymorphism in *COMT* [4].

Catechol-*O*-methyltransferase (COMT) methylates neurotransmitters such as dopamine and noradrenaline, and drugs such as L-dopa. *COMT* is located in q11.21 on chromosome 22 and has various single nucleotide polymorphisms (SNPs). One base of the 108/158th codon replaces G with A, which changes valine to methionine[5]. The activity of the Val allele enzyme is 3- to 4-fold higher than that of the Met allele enzyme[6], and this SNP may affect the dynamics of neurotransmitters and the

antipsychotic response. A recent meta-analysis showed that individuals with Met/Met genotype were associated with favorable response to atypical antipsychotics[4]. This meta-analysis included both positive[7-10] and negative[11-14] studies regarding the association between the Val 108/158 Met genotype and treatment response to antipsychotics. However, the meta-analysis did not include studies with aripiprazole, which has unique pharmacological profile as a partial agonist for dopamine D2 receptors. Furthermore, underlying biological basis of the association between the Val 108/158 Met genotype and treatment response to antipsychotics remains unclear.

Homovanillic acid (HVA) and plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) are main metabolites of dopamine and noradrenaline, respectively. Plasma levels of HVA and MHPG reflect 30-50% of HVA[15] and one-third of MHPG[16] in the central nervous system, respectively. Although it is difficult to regard plasma monoamine metabolites as direct reflections of central nervous system activity, plasma HVA levels are considered a possible indicator of the clinical response to antipsychotic drugs[17]. Furthermore, plasma HVA levels parallel improvement in positive symptoms during treatment of schizophrenia[18].

Because no studies have examined the association between the *COMT* Val 108/158 Met polymorphism and treatment response to aripiprazole and the genotype effects on

monoaminergic neurotransmission during antipsychotic treatment remains unknown, we investigated the effects of the *COMT* Val 108/158 Met polymorphism on treatment response to aripiprazole and on plasma monoamine metabolite levels in patients with acute schizophrenia.

Materials and Methods

The subjects were Japanese patients who were diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Subjects included both drug-naïve and drug-free recurrent patients who had received no antipsychotic drugs (neither oral nor long-acting injection) for at least 2 weeks before entry into this study. For inclusion in this study, patients had to have a Positive and Negative Syndrome Scale (PANSS) total score of at least 80 and minimum score of 4 on at least two psychotic item subscales (hallucination, delusion, conceptual disorganization, and suspiciousness). Patients who abused alcohol/drugs and/or those who had organic brain disorders were excluded. Patients received 18 mg/day aripiprazole on day 1. From day 2 to the endpoint, physicians regulated the doses of aripiprazole carefully based on the clinical symptoms. Benzodiazepines and anticholinergics were permitted as additional medications to manage insomnia, restlessness, and extrapyramidal symptoms. The efficacy of the treatment was evaluated using PANSS, the Clinical Global Impression (CGI)-S (Severity), and -CGI-I (Improvement) Scale. Patients with a CGI-I score of 1 or 2 or a ≥30% decrease from baseline in the PANSS total score were defined as responders.

Blood samples were obtained before breakfast at 0 and 6 weeks after aripiprazole

administration. Concentrations of plasma monoamine metabolites were analyzed with high-performance liquid chromatography (HPLC) with electrochemical detection. Plasma levels of HVA and MHPG were analyzed using the methods of Watanabe et al. [19]. The intra-assay coefficients of variation for plasma HVA and MHPG in our laboratory were 3.2% and 3.1%, respectively. The inter-assay coefficients of variation for plasma HVA and MHPG were 8.6% and 7.6%, respectively. Genomic DNA was extracted from white blood cells from patients, and the Val 108/158 Met genotype in *COMT* was determined with the polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) method as previously described[20]. The GeneAmp PCR System 9700 was used to amplify COMT DNA. The primer pairs were the same as in a previous study[20]. The amplification program included initial denaturation at 95°C for 3 min, followed by 30 cycles of 58°C for 30 seconds, 72°C for 1 min, and 95°C for 30 seconds, followed by a final extension at 72°C for 10 min. Nla III was added to the PCR products (217 bp), and samples were incubated at 37°C for 60 min. Samples were then electrophoresed on 4% agarose gels (Wako Agarose Xp, Wako, Osaka, Japan) and visualized with UV. Following amplification and Nla III digestion, the Val/Val genotype yielded bands of 136 and 81 bp, Val/Met yielded bands of 136, 96, 81, and 40 bp, and Met/Met yielded bands of 96, 81, and 40 bp. This study was approved by the ethics

committee of Fukushima Medical University, and the patients provided written informed consent after having been informed of the purpose of the study.

We investigated the genotype effects on treatment response (responder rate and changes in PANSS scores) and on plasma levels of monoamine metabolites. Furthermore, we performed responder versus non-responder comparison. One-way analysis of variance (ANOVA) was used to compare the patient's demographics (age, duration of illness, etc.), each PANSS score, and the plasma levels of HVA and MHPG among genotypes. The $\chi 2$ test was used to compare the sex ratio. The last observation carried forward (LOCF) method was used when a dropout occurred. Repeated measures ANOVA was used to compare the genotypes, treatment period, changes in the PANSS score, and plasma monoamine metabolite levels. The significance level was defined as a $p<0.05$. All statistical analyses were performed using IBM SPSS Statistics 23.

Results

Of the 40 patients, 39 patients completed the study, and one patient dropped out at week 4 because of a lack of efficacy based on the physician's clinical decision. Among the 40 patients, 16 (40.0%) were responders (Supplementary Table 1). At the endpoint, doses of aripiprazole ranged from 9 to 30 mg/day (mean ± SD = 24.33 ± 6.33 mg/day). Of the 40 patients, 29 (72.5%) received benzodiazepines (Val/Val: n=18 (5-18.3mg/day), Val/Met: n=9 (4.2-22.5mg/day), Met/Met: n=2 (5mg/day) (doses were converted to diazepam equivalents), and 10 (25%) received biperiden (Val/Val: n=6 (2-3mg/day), Val/Met: n=4 (1-4mg/day), Met/Met: n=0). In responders, aripiprazole decreased plasma levels of HVA ($p = 0.015$), whereas the drug did not change plasma HVA levels ($p = 0.418$) in non-responders. The plasma levels of MHPG decreased in both responders ($p = 0.001$) and non-responders ($p = 0.038$). Of the 40 patients, 23 patients were homozygous for Val, 13 were heterozygous, and four were homozygous for Met. The allele distribution was in Hardy-Weinberg equilibrium ($\chi^2 = 0.98$, df = 1, $p > 0.05$). At baseline, no significant differences in PANSS scores, CGI-S, or plasma levels of monoamine metabolites were found (Table 1).

The responder rate to aripiprazole did not differ among the three genotype groups ($p = 0.157$) (Table 1). Repeated measures ANOVA revealed significant time effects on

PANSS total ($p < 0.001$) and positive ($p < 0.001$) and negative ($p < 0.001$) scores (Figure 1). There were significant genotype - time interactions on PANSS total ($p = 0.009$) and general psychopathology ($p = 0.007$) scores, with Met/Met genotype showing greater improvement (Figure 1). We also found a trend level genotype - time interaction in the PANSS negative score ($p = 0.065$).

We found a significant time effect on plasma MHPG levels ($p = 0.009$), but no time effect was found for plasma HVA levels ($p = 0.756$) or time - genotype interactions on plasma levels of HVA ($p = 0.21$) or MHPG ($p = 0.47$).

Table 1. Comparisons among the three genotypes

	Val/Val group (n=23)	Val/Met group (n=13)	Met/Met group (n=4)	p value
at baseline				
age (years)	41.6±11.9	43.5±14.2	35.7±2.1	0.621[a]
sex, male/female	13/10	9/4	3/1	0.648[b]
duration of illness (years)	10.0±9.6	13.7±14.2	8.0±7.0	0.576[a]
PANSS total	105.1±13.2	109.5±15.1	113.8±10.6	0.412[a]
PANSS positive	28.1±4.9	28.5±3.5	27.3±2.5	0.867[a]
PANSS negative	23.8±5.6	24.8±6.4	28.3±6.5	0.390[a]
PANSS general	53.2±7.7	55.9±9.3	59.5±7.2	0.305[a]
CGI-Severity	5.5±0.5	5.5±0.8	5.5±0.6	0.983[a]
plasma HVA level (ng/ml)	17.0±7.1	19.1±7.9	14.1±5.6	0.455[a]
plasma MHPG level (ng/ml)	11.3±5.3	13.9±7.6	7.9±3.3	0.195[a]
at endpoint				
dose of aripiprazole (mg/day)	22.0±7.4	26.8±4.0	26.0±3.5	0.097[a]
Responders/non-responders	10/13	3/10	3/1	0.157[b]
PANSS total	83.5±17.8	92.2±22.1	67.3±24.0	0.094[a]
PANSS positive	20.6±6.5	23.0±7.0	14.8±5.9	0.107[a]
PANSS negative	20.6±5.5	22.2±6.8	20.3±9.2	0.734[a]
PANSS general	42.3±8.1	46.9±11.8	33.3±12.3	0.058[a]
CGI-Severity	3.8±1.4	4.2±1.4	2.5±1.7	0.119[a]
CGI-Improvement	2.7±1.1	3.0±1.1	1.5±1.0	0.061[a]
plasma HVA level (ng/ml)	16.8±11.0	15.4±7.4	19.6±10.6	0.759[a]
plasma MHPG level (ng/ml)	7.9±3.3	8.6±3.9	6.5±1.9	0.552[a]

PANSS, Positive and Negative Syndrome Scale; CGI, Clinical Global Impression;
HVA, homovanillic acid; MHPG, 3-methoxy-4hydroxyphenylglycol.

[a]One-way analysis of variance (ANOVA)

[b]Pearson's $\chi 2$ test

Supplementary Table 1. Comparisons between responders and non-responders

	Responders (n=16)	Non-responders (n=24)	p value
at baseline			
age (years)	40.3±12.0	42.9±12.1	0.644[a]
sex, male/female	8/8	17/7	0.182[b]
duration of illness (years)	11.8±11.1	10.9±11.2	0.981[a]
PANSS total	107.1±9.2	107.6±16.1	0.053[a]
PANSS positive	27.5±3.8	28.6±4.5	0.750[a]
PANSS negative	24.9±4.2	24.4±6.9	0.080[a]
PANSS general	54.6±7.3	54.8±9.0	0.359[a]
CGI-Severity	5.6±0.5	5.5±0.7	0.214[a]
plasma HVA level (ng/ml)	17.1±6.5	17.6±7.8	0.466[a]
plasma MHPG level (ng/ml)	11.5±6.0	12.0±6.3	0.608[a]
at endpoint			
dose of aripiprazole (mg/day)	21.3±6.2	26.4±5.7	0.618[a]
Genotype groups (ValVal / ValMet / MetMet)	10/3/3	13/10/1	0.157[b]
PANSS total	67.8±10.1	96.0±17.9	0.046[a]
PANSS positive	15.1±3.2	24.5±5.9	0.009[a]
PANSS negative	17.8±2.9	23.3±6.9	0.020[a]
PANSS general	34.9±5.5	48.3±9.2	0.056[a]
CGI-Severity	2.6±0.7	4.7±1.2	0.006[a]
CGI-Improvement	1.5±0.5	3.5±0.5	0.000[a]
plasma HVA level (ng/ml)	12.7±3.7	19.3±11.5	0.006[a]
plasma MHPG level (ng/ml)	6.3±1.8	9.1±3.8	0.004[a]

PANSS, Positive and Negative Syndrome Scale; CGI, Clinical Global Impression; HVA, homovanillic acid; MHPG, 3-methoxy-4hydroxyphenylglycol.

[a]Student's *t* test (unpaired)

[b]Pearson's $\chi 2$ test

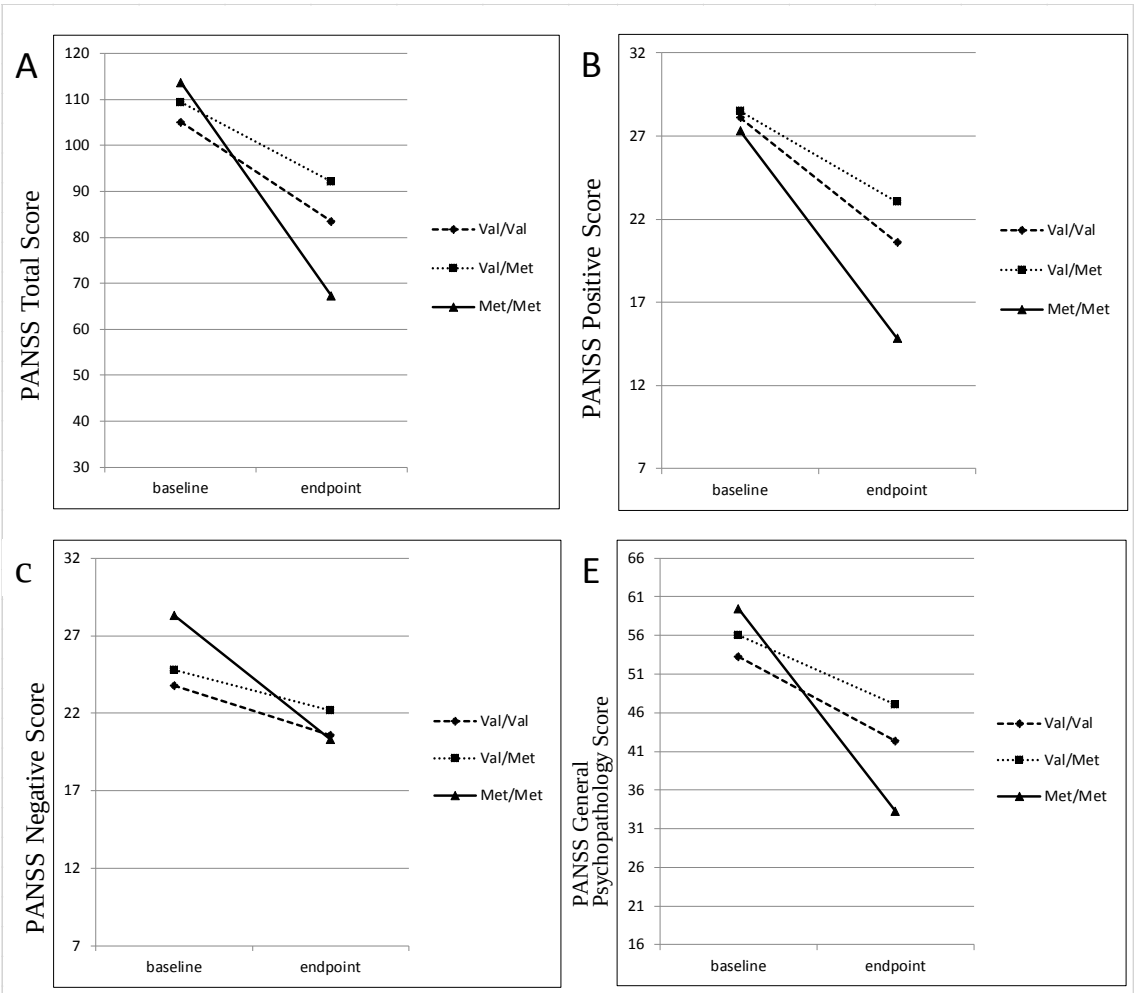

FIGURE 1. A Mean change in PANSS Total, Positive, Negative and General Psychopasology Scores at baseline and 6 weeks.
A, genotype × time interactions on PANSS Total Score ($F = 5.296$; $p = 0.009$). B, genotype × time interactions on PANSS Positive Score ($F = 2.493$; $p = 0.096$). C, genotype × time interactions on PANSS Negative Score ($F = 2.941$; $p = 0.065$). E, genotype × time interactions on PANSS General psychopathology Score ($F = 5.741$; $p = 0.007$) .

Discussion

To the best of our knowledge, this is the first study to investigate the effects of the Val 108/158 Met polymorphism in *COMT* on treatment response to aripiprazole and plasma monoamine metabolite levels in patients with acute schizophrenia. Although the responder rate did not differ among the three genotype groups, we found a significant association between the Val 108/158 Met polymorphism and the improvement in PANSS score after the treatment with aripiprazole. On the other hand, no significant genetic effects were found on plasma levels of monoamine metabolites during treatment.

Our results showing a significant relationship between the Met/Met genotype and greater improvement in PANSS score are consistent with a recent meta-analysis[4] demonstrating that Met/Met individuals show significantly greater improvements than Val carriers, although the meta-analysis included studies of typical and atypical antipsychotics, but not aripiprazole. Notably, the meta-analysis reported no significant associations between the Val 108/158 Met polymorphism and treatment response in patients treated with typical antipsychotics. Although aripiprazole has a different pharmacological profile than other antipsychotics as a partial agonist for DRD2, aripiprazole is classified as an atypical antipsychotic drug, and our results support the

results of Huang et al.[4].

The difference in treatment response among the genotypes may be partially explained by the enzyme activity of COMT. The activity of the Val allele enzyme is 3- to 4-fold higher than that of the Met allele enzyme[6]. If individuals with the Met/Met genotype have lower COMT activity, dopamine will not be metabolized sufficiently, which may lead to hyperdopaminergic neurotransmission. In such a case, antipsychotics may inhibit the hyperdopaminergic state with antagonism for DRD2 in the mesolimbic system more effectively in the acute phase of schizophrenia, although we found no significant genotype - time interaction on PANSS positive score. Furthermore, the inverted U-curve hypothesis of dopamine function suggests that too much dopamine activity in the prefrontal cortex impairs working memory performance, whereas hypofunction of dopamine leads to cognitive dysfunction in patients with schizophrenia[21]. Atypical antipsychotics including aripiprazole have inhibitory effects on DRD2 and also 5-HT2A receptors, which may be related to appropriate dopamine neurotransmission in the prefrontal cortex. On the other hand, typical antipsychotics inhibit DRD2 but not 5-HT2A receptors, which may induce hypofunction of dopamine. Additionally, aripiprazole is a partial agonist for DRD2, which may also stabilize dopamine function in the prefrontal cortex. Taken together, Favorable response to

aripiprazole in patients with the Met/Met genotype may be explained by stabilizing dopamine function in the prefrontal cortex, which lead to improve cognitive function.

In this study, the Val 108/158 Met polymorphism was not associated with changes in plasma levels of monoamine metabolites. Previous studies had reported that the Val 108/158 Met polymorphism is not associated with monoamine metabolites levels in cerebrospinal fluid[22-24] or plasma[25-27], although no studies examined the association between the polymorphism and changes in levels of monoamine metabolites during treatment with antipsychotics. Our results suggest that the Val 108/158 Met polymorphism may not be related to changes in plasma levels of HVA or MHPG after aripiprazole treatment in schizophrenia. We previously reported associations between variants in *DRD2* and plasma levels of monoamine metabolites[17, 28], suggesting that Taq1A polymorphism in *DRD2* may have effects on plasma HVA levels[17]. COMT metabolizes dopamine and other monoamines, and is not directly affected by antipsychotics. Therefore, the Val 108/158 Met polymorphism may not have effects on plasma levels of HVA or MHPG as do *DRD2* polymorphisms.

Our study has several limitations. First, our sample size was very small, there were only 4 subjects in Met/Met genotype group. This limitation restricts our preliminary results. Second, this study included both first episode and recurrent patients. Recurrent

patients may be influenced by previous treatment effects such as upregulation of D2 receptors. Third, this study focused on only a *COMT* polymorphism, and we did not examine gene-gene interactions. Finally, we did not examine cognitive functions such as working memory with a neuropsychological test battery. Nevertheless, this is the first study to investigate the effects of the Val 108/158 Met polymorphism in *COMT* on treatment response to aripiprazole, and our results showed that individuals with the Met/Met genotype had greater improvement in PANSS score after the treatment. Further studies should investigate the underlying biological mechanism of the association between the Met/Met genotype and a favorable response to antipsychotics.

Conclusion

In conclusion, we found a significant association between the Val 108/158 Met polymorphism in *COMT* and the improvement in PANSS score after the treatment with aripiprazole. Although the responder rate did not differ among the three genotype groups, individuals with the Met/Met genotype had greater improvement in PANSS score after the treatment. On the other hand, the Val 108/158 Met polymorphism may not affect plasma levels of HVA or MHPG. Caution is needed when interpreting our results because of the small sample size and heterogeneity among patients. Additional

studies with a larger sample size are needed to confirm and extend our results.

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